REMARKS

Overview

In the Office Action under reply, claims 22-31 and 39-52 are pending and were examined, claims 1-21 and 32-38 having been canceled previously. The claims stand rejected as follows:

(1) claim 51 is rejected under 35 U.S.C. § 112, first paragraph;

(2) claims 42-43 and 49 are rejected under 35 U.S.C. § 112, second paragraph;

(3) claims 22-30, 40-44, and 48-52 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong et al., US 5,560,933 ("Soon-Shiong");

(4) claims 31 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong in view of Russell et al., *Bone Marrow Transplantation* (1999) 24, pp. 1177-1183 ("Russell") and further in view of Vook et al., US 2003/0129233 ("Vook").

In addition, claims 45-47 are objected to as being dependent upon a rejected base claim. Applicants acknowledge with appreciation that the Examiner identifies these claims as allowable if rewritten as independent claims.

The rejections and objections are overcome in part by the amendments made herein, and are otherwise traversed for at least the reasons set forth below.

Claim amendments

With the amendments made herein, claim 22 is amended to recited targeted delivery of the therapeutic agent within the central nervous system of the subject. Support for this amendment can be found, for example, in applicants' original specification on page 2, line 30 to page 3, line 3. Claim 49 is amended to remove the options of a liquid or a combination of liquid and gas. Claim 51 is canceled, and the dependency of claim 52 has been adjusted. No new matter is added by these amendments.

New claims 53 and 54 are added. These claims are supported by the language of claim 22. No new matter is added.

Rejection under 35 U.S.C. §112, first paragraph

Claim 51 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. With this submission, claim 51 has been canceled. The rejection is therefore moot.

Rejection under 35 U.S.C. §112, second paragraph

Claims 42, 43, and 49 are rejected under 35 U.S.C. §112, second paragraph as indefinite. Regarding claims 42 and 43, the Action states that "[t]he term 'about' is not defined by Applicants' specification" (Action at 3). Applicants traverse this rejection at least for the following reasons. According to MPEP § 2173.05(b), "When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree." Applicants' specification provides guidance as to the meaning of the term "about" in the context of buoyancy within the cerebral spinal fluid (CSF). For example, page 10, line 27 to page 11, line 2, states that "[t]he specific gravity (SG) of CSF is normally about 1.0063 gm/ml to about 1.0075 gm/ml, although those skilled in the art will recognize that the specific gravity of CSF may vary individually between subjects." Thus, the skilled artisan would understand that the term "about" in claims 42 and 43 is used in the context of buoyancy in the CSF of a subject.

Regarding claim 49, the Action states that "a liquid" has insufficient antecedent basis. With this submission, the term "liquid" is removed from claim 49. The rejection is therefore moot.

Rejection under 35 U.S.C. §103(a)

Claims 22-30, 40-44, and 48-52 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong. The rejection is traversed.

<u>The legal standard</u>

A rejection under 35 U.S.C. § 103 requires the following analysis: "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved" *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Then, "the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference

teachings establish a *prima facie* case of obviousness) is more probable than not" (MPEP § 2142). The Action fails to meet this standard. As shown by the arguments set forth below, the preponderance of the evidence suggests that Soon-Shiong does not provide a prima facie case of obviousness.

Applicants' claims

The instant claims recite a method comprising intrathecally administering a composition to the central nervous system of a subject. The composition comprises a plurality of biodegradable polymer particles having a therapeutic agent and a buoyancy agent contained therein, and the composition is controllably buoyant within the cerebrospinal fluid. The buoyancy agent is a gas or an oil, or a combination of a gas and an oil. Such a method is not disclosed in Soon-Shiong.

The applied reference

Soon-Shiong is directed to *in vivo* delivery of substantially water insoluble active agents in which the active agent is delivered in a soluble form or in the form of suspended particles (Soon-Shiong, Abstract).

1. Improper Use of Hindsight and Lack of Expectation of Success

The Action rebuts applicants' previous argument that the Examiner's conclusion is based on improper hindsight reasoning by stating that "any judgment of obviousness is in a sense necessarily a reconstruction based on hindsight reasoning" (Action at 10). The Action then states that such hindsight reasoning is proper "so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made" (Id.). The Action fails, however, to show that all of the knowledge necessary to devise applicants' invention was present in Soon-Shiong and/or the ordinary skill at the time applicants' invention was made. Specifically, the disclosure of Soon-Shiong does not teach that vegetable oil (or, in fact, any oil whatsoever) is suitable for administration to the CSF and can be used as a buoyancy agent therein. Furthermore, the Examiner does not point to any evidence that would support the conclusion that the skilled artisan, at the time of the instant invention, would have known that vegetable oil can be administered to the CSF.

Even assuming, *arguendo*, that the skilled artisan knew that vegetable oil could be

administered to the CSF as part of a therapeutic formulation (or could deduce this information from Soon-Shiong), there is no evidence that there would have been a reasonable expectation of success for obtaining a formulation that is controllably buoyant within the CSF. Such an expectation is required, as set forth in MPEP § 2143.02(I): "[t]he prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)." In fact, the skilled artisan would not have had such an expectation of success, as evidenced by the Declaration of Dr. Peter Jarrett attached to this response (discussed in more detail below).

2. Different Function in Soon-Shiong

The Action rebuts applicants' previous arguments by stating that "the prior art is not required to recite the same motivation that induced Applicants' to develop their claimed invention" (Action at 11). However, the cited reference must teach the same function for each of the components of the claimed invention. The MPEP states:

> [a] rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. [398], 82 USPQ2d 1385, 1395 (2007)

(MPEP § 2143.02, emphasis added). As described previously by applicants, and as further described in the Declaration of Dr. Peter Jarrett attached to this response, the vegetable oil in Soon-Shiong is used in the manufacturing process as a dispersing agent to suspend active agent within the pharmaceutical formulation. Soon-Shiong does not teach formulations whereby vegetable oil is used as a buoyancy agent. In fact, the pharmaceutical formulations taught in Soon-Shiong would not be predicted or expected by the skilled artisan to be controllably buoyant within the CSF.

3. Evidence Supporting Non-Obviousness

In support of the foregoing statements, applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Peter Jarrett, a recognized expert in the field of drug formulations and drug delivery systems. Dr. Jarrett's statements also support the remarks made in applicants' previous response submitted January 30, 2009, the contents of which are incorporated herein by reference.

Dr. Jarrett's declaration supports the conclusion that the skilled artisan would not have thought to use the dispersing agent and particles from Soon-Shiong as a buoyancy-controlled composition for targeted administration in the CNS. Furthermore, the declaration states that, even if such a use had been envisioned, the skilled artisan would not have had a reasonable expectation of success. Due to the specific properties of the Soon-Shiong compositions, targeted delivery within the CNS via a controllably buoyant composition would not be expected based on the disclosure of Soon-Shiong (*see, e.g.*, paragraph 10 in Dr. Jarrett's declaration).

According to MPEP § 2143.02(II), "[e]vidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." Dr. Jarrett's declaration is evidence of a lack of expectation of success. Dr. Jarrett's declaration is also evidence that the skilled artisan would not have found the instant invention obvious in view of the disclosure of Soon-Shiong.

For at least the foregoing reasons, applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §103(a)

Claims 31 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong in view of Russell and further in view of Vook.

Soon-Shiong is discussed above.

The Action states that "Soon-Shiong lacks the teachings of an intrathecal administration method, wherein the active agent consists of living cells," and contends that the deficiency of Soon-Shiong is cured by the teachings of Russell. The Action also states that "Soon-Shiong lacks the teachings of an intrathecal administration method, wherein the biodegradable polymer is PLGA," and contends that the deficiency of Soon-Shiong is cured by the teachings of Vook.

Without commenting on whether Russell or Vook cure the deficiencies just noted, applicants' traverse the rejection because neither reference discloses the use of buoyancy agents in delivery of therapeutic agents to the CNS. Accordingly, the combination of Soon-Shiong with Russell and Vook fail to provide a prima facie case of obviousness for claim 22 and claims depending from claim 22 (i.e., claims 31 and 39). Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants submit that the claims of the application are in condition for allowance. Applicants respectfully request withdrawal of the rejections, and prompt issuance of a notice of allowance. If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, a telephone call to the undersigned would be welcomed.

Respectfully submitted,

/Isaac M. Rutenberg/

By: _____

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